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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 06/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/802,955	MICHAL ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-8,19-22 and 63-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-8,19-22 and 63-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments filed 17 April 2006 to claims 1, 3, 5-8, 19-20 and 22 have been entered. Claims 2, 4, 9-18, and 23-62 are cancelled. New claims 63-68 have been added. Claims 1, 3, 5- 8, 19-22 and 63-68 are pending in the current application, all of which have been considered on the merits.

Priority

Acknowledgement is made of applicant's claim for status as a CIP of copending application 10/414,602, filed 04/15/2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-22, 63-65, 67 and 68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have amended claim 19 so as to now require application of a pacing therapy to the ventricle to pre-excite the infarct region to contract during systole at a time before contraction of the ventricle initiated by the His Purkinjec conduction network, such a limitation is not supported by the disclosure as originally filed, and thus is considered new matter.

In their response applicants point to paragraph 0070 for support for the amendment, but neither paragraph 0070 nor the remainder of the specification teach applying the pacing therapy to the ventricle

during systole at a time before contraction of the ventricle. Paragraph 0070, and the surrounding section, discuss the electrical system in the heart and do suggest treating a ventricular region to induce contraction earlier than parts of the ventricle to decrease preload and afterload stress; however, there is no support for specifically applying the therapy during systole. An amendment to the claims or the addition of a new claim must be supported by the description of the invention in the application as filed. In re Wright, 866 F.2d 422, 9 USPQ2d 1649 (Fed. Cir. 1989). Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 5-8, 19-22 and 63-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claims 1-8 are directed to a method, comprising identifying an infarct region within the ventricle of a human subject; and percutaneously delivering alpha-1,3-galactosyltransferase (GGTA1) knock-out swine cells to the infarct region within the ventricle of the human subject, wherein the knock out swine cells stimulate a beneficial response within the ventricle.

Applicants' claim 1 does not have a proper preamble, rather the preamble is merely "A method," with no identification of intended purpose or use. Though steps are recited in the method, the claims are found indefinite because one cannot determine what they are intended to accomplish.

Furthermore, in claim 1, applicants have added a limitation requiring the alpha-1,3-galactosyltransferase (GGTA1) knock-out swine cells do not express alpha-1,3-galactosyltransferase;

however, by the nature of the cells being GGTA1 *knock-out* cells, they inherently do not express GGTA1. Therefore, such a limitation is not necessary, and rather only confuses the claim.

Still further in claim 1, applicants have amended the claim to require the knock-out swine cells to 'stimulate a beneficial response' within the ventricle. It is not clear what this 'beneficial response' is or how it is stimulated; therefore appears stimulation of a beneficial response is inherent due to percutaneous delivery of GGTA knock-out cells.

In claim 3, there is insufficient antecedent basis for the limitation "the donor cells" in the first line of the claim. Also, it is unclear if the "a donor cell" recited in line three of the claim is the same as "the donor cell" recited in the first line, or if they are each different types of cells. It appears applicant intends to refer to the GGTA1 knock-out swine cells, examination has been conducted as such.

Furthermore, in claim 3, the amendment now only requires both chromosomal copies of *a* gene to be disrupted, it is not required that both chromosomal copies of the GGTA1 gene have been disrupted, as was previously required. It is not clear what gene must be disrupted in the diploid cells, for purposes of examination it is being considered that the GGTA1 gene must be disrupted.

In claim 5 the term "donor cells" appears, yet there are no donor cells recited in parent claim 1, it appears applicant intends to refer to the GGTA1 knock-out swine cells. Furthermore, it is unclear what 'amount' is required to 'structurally reinforce the infarct region.' The phrase renders the claim indefinite, because the 'amount' of cells required is used in reference to an object that is variable: structural reinforcement of the infarct region. One cannot determine the amount of cells required to satisfy the limitation "to structurally reinforce the infarct region" because structural reinforcement is measured on a continuous scale, as few as one or two cells could be construed to provide some degree of structural reinforcement, whereas complete repopulation of the infarcted region with thousands of cells would provide superior structural reinforcement. In general, a relative term (such as an amount required to perform/accomplish a final result) can only be construed as definite when the final product/result (in this

case the degree of structural reinforcement) is made clear; a relative term cannot be used in reference to a variable object/result, as the metes and bounds of the claim cannot then be determined.

Claim 6 recites the limitation "the donor cells" in the first line of the claim, there is insufficient antecedent basis for this limitation in the parent claim. For purposes of examination, the GGTA1 knock-out cells are being interpreted as the 'donor cells.'

Claim 7 recites the limitation "the donor cells" in the 1^{st}-2^{nd} lines of the claim, there is insufficient antecedent basis for this limitation in the parent claim. For purposes of examination, the GGTA1 knock-out cells are being interpreted as the 'donor cells.'

Claim 8 recites the limitation "the donor cells" in the second line of the claim, there is insufficient antecedent basis for this limitation in the parent claim. For purposes of examination, the GGTA1 knock-out cells are being interpreted as the 'donor cells.' Claim 8 also remains awkward, it would be remedial to claim "wherein the 'donor cells' contain a nucleic acid encoding a detectable polypeptide, wherein the detectable polypeptide is operably linked to a promoter."

Claim 67 recites the limitation "the donor cells" in the first line of the claim, there is insufficient antecedent basis for this limitation in the parent claim. For purposes of examination, the GGTA1 knock-out cells are being interpreted as the 'donor cells.'

Applicants amended claim 19 is directed to a method comprising identifying an infarct region within a ventricle of a subject; applying a pacing therapy to the ventricle to pre-excite the infarct region to contract during systole at a time before contraction of the ventricle initiated by the His Purkinje conduction network; and percutaneously delivering at least one structurally reinforcing component to the infarct region after applying the pacing therapy.

Applicants' claim 19 does not have a proper preamble, rather the preamble is merely "A method," with no identification of intended purpose or use. Though steps are recited in the method, the claims are found indefinite because one cannot determine what they are intended to accomplish.

Furthermore, in claim 19 the term "structurally reinforcing component" does not clearly define what is intended to be percutaneously delivered to the infarct region. The term "structurally reinforcing component" covers a large variety of agents and components, ranging from biological agents, such as the GGTA1 cells of claim 20, to synthetic polymers or other agents associated with the term "structural support/reinforcing". It is recognized that the specification teaches various agents that may be delivered to the infarct region, the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore the claims are not deemed to correspond to the scope of the specification, as the term "structurally reinforcing agent" covers a much broader scope than the specification. Clarification of the term is required to more clearly define the metes and bounds of the claimed invention.

Applicants have amended claim 22 to require the method of claim 19 to further comprise modifying the pacing therapy based upon a sensed measurement. It remains unclear what the 'sensed measurement' is of, how it is taken, or how the pacing therapy is modified in response to the measurements. New claims 63-65 are also directed to 'the sensed measurement' but do not clarify how these measurements are taken or how the pacing therapy is modified based on the measurements.

Claim 67 recites the limitation "the donor cells" in the first line of the claim, there is insufficient antecedent basis for this limitation.

First it is noted that the article "an" is inappropriate at the fourth line of claim 19 "delivering ~~an~~ at least one structurally reinforcing component". Second, the phrase "unload the infarct region from mechanical stress" is unclear.

New claim 68 requires the structurally reinforcing component to have a property that stimulates a healing response in the ventricle. It is unclear what the structurally reinforcing agent is or what the healing response is. Therefore applicants have failed to particularly point out and claim their invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5-8 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dinsmore (US Patent 5,979,449), in view of Gustafsson et al (US Patent 6,153,428), and further in view of Strauer et al (Circulation, 2002) and Etzion et al (J Mol Cell Cardiol, 2001).

Applicant's claim 1 is directed to a method, comprising identifying an infarct region within the ventricle of a human subject; and percutaneously delivering alpha-1,3-galactosyltransferase (GGTA1) knock-out swine cells to the infarct region within the ventricle of the human subject, wherein the knock out swine cells stimulate a beneficial response within the ventricle. Claim 3 requires the GGTA1 knock-out swine cells (donor cells) to be diploid, and for both chromosomal copies of a gene to have been disrupted. Claim 5 is directed to the method of claim 1, wherein a sufficient amount of GGTA1 knock-out swine cells (donor cells) are delivered to the infarct region to structurally reinforce the infarct region. Claim 6 requires the GGTA1 knock-out cells (donor cells) to replace damaged cells in and around the infarct region. Claim 7 requires the delivery of the GGTA1 knock-out cells (donor cells) to occur within 2 weeks of a myocardial infarction (MI). Claim 8 requires the GGTA1 knock-out cells (donor cells) to carry a nucleic acid encoding a detectable polypeptide operably linked to a promoter. Claim 66 requires the GGTA1 knock-out (donor) cells to be stem cells.

Dinsmore teaches a method for treating cardiac disorders in humans, including myocardial ischemia, by implantation of porcine cardiomyocytes into the damaged myocardium (See Dinsmore, col. 3, ln 23-55). While Dinsmore does not specifically state a first step of identifying an infarct region within the human subject in need of the cell treatment, one of ordinary skill in the art will recognize that such a first step is routine in the practice of myocardial treatment as it is necessary to determine the type and extent of cardiac damage; means of identifying the infarcted region are well known in the art and include heart catheterization, coronary angiography and/or left ventriculography (See Strauer et al, Pg. 1914, col. 1). Therefore, while Dinsmore does not explicitly state such a first step, such identification would be an obvious routine first step for quality treatment and patient safety.

Dinsmore teaches porcine cardiomyocytes are the preferred tissue donor source for xenotransplantations to humans when syngeneic human tissue is unavailable, due to greater availability of swine tissue compared to human tissue, similarity in organ size between the tissues, reduced risk of zoonotic infections and reduced ethical concerns (See Dinsmore, col. 1-2). Dinsmore teaches transplantation of porcine cardiomyocytes into the heart of a human subject results in replacement of lost cardiomyocytes. About 10^6-10^7 porcine cardiomyocytes can be introduced into the human heart; such an amount is sufficient to at least partially reduce or alleviate at least one adverse effect or symptom of the cardiac disorder (which is being considered sufficient to stimulate a beneficial response within the ventricle & sufficient to structurally reinforce the infarct region).

Dinsmore recognizes xenotransplantations run a high risk of immunorejection due to species-specific antigens; therefore in order to reduce the risk of immunorejection of the swine cardiomyocytes Dinsmore suggest altering the cardiomyocyte such that an antigen on the cardiomyocyte surface which is capable of stimulating an immune response is altered to inhibit rejection of the cardiomyocyte upon introduction into the human subject (See Dinsmore, abstract & col. 9, ln 56-col. 24). In one embodiment Dinsmore teaches altering the Gal(α1,3)Gal epitope, either by removal or the epitope from the surface of

the cells by enzymatic or chemical cleavage or by inhibiting the formation of the epitope by inhibiting the activity of an alpha-1,3-galactosyltransferase within the cell.

Therefore, based on the teaching of Dinsmore to inhibit the formation of the Gal(α1,3)Gal epitope on the cell surface to reduce potential immunorejection, it would have been well within the purview of one of ordinary skill in the art at the time the invention was made to go one step further so as to use α-1,3-galactosyltransferase (GGTA1) knock-out swine cells, wherein both copies of the GGTA1 gene have been disrupted. Such GGTA1 knock-out swine cardiomyocytes were known at the time of the invention, for example, Gustafsson et al (See Gustafsson et al col. 2, ln 19-33 & col. 6, ln 2-5). GGTA1 knock-out swine cells that have both copies of the GGTA1 gene have been disrupted cannot produce any GGTA1, and thus cannot form the antigenic Gal(α1,3)Gal epitopes at all. Clearly one of ordinary skill in the art will recognize that use of GGTA1 knock-out cells would provide superior inhibition of the antigenic Gal(α1,3)Gal epitopes compared to the methods of Dinsmore, which involve suppression of the GGTA1 gene or inhibition of the alpha-1,3-galactosyltransferase enzymes, as the knock-out cells are incapable of producing the epitopes, whereas the as the methods of Dinsmore only provide reduced epitope formation. One would expect success using the GGTA1 knock-out swine cardiomyocytes of Gustafsson in the method of Dinsmore because Gustafsson teaches the transgenic GGTA1 knock-out cells can be used as a source of cells for xenotransplantation (See Gustafsson et al, col. 5, ln 58-col. 6, ln 9).

Regarding the means of cell delivery, Dinsmore teaches the porcine cardiomyocytes can be delivered to the subject by any appropriate route; specifically they suggest direct injection into the ventricular myocardium or injection through use of tubes, catheters, etc (See Dinsmore, col. 13, ln 19-64). In the examples Dinsmore teaches direct injection during open chest surgery (See Dinsmore, Example 2, col. 19-20). However, in order to reduce the invasiveness and risk associated with open heart surgery, it would have been obvious to one of ordinary skill in the art to alternatively deliver the cells via percutaneous transluminal coronary angioplasty (PTCA). Strauer et al teach PTCA is desirable for

delivering cells to infarcted myocardium in human patients because it allows the maximum amount of cells to contact and enrich the infarct tissue and peri-infarct zone during a single treatment (See Strauer et al, Pg. 1917, col. 1). Therefore, based on the teachings of Strauer et al, it would have been obvious to one of ordinary skill in the art to deliver the GGTA1 knock-out swine cardiomyocytes to the infarcted region via percutaneous transluminal coronary angioplasty; one would have expected success because Strauer et al teach PTCA is superior to intraventricular injection and it is less invasive then direct injection during open-heart surgery.

Dinsmore is silent with regards to the time period in which the xenotransplantation should occur after the myocardial infarction; however, Strauer et al clearly teach that the optimal time point for cell transplantation is between 7 and 14 days post myocardial infarction, as after 14 days scar formation reduces the benefit of cell transplantation (See Strauer et al, Pg. 1917, col. 2). Therefore, one of ordinary skill in the art would have been motivated to perform the xenotransplantation of the GGTA1 knock-out swine cardiomyocytes between day 7 and 14 after MI, based on the teachings of Strauer et al, in order to ensure maximum uptake and integration of cells into the infarct zone.

Still further, though Dinsmore focuses on delivery of cardiomyocytes, Strauer et al provides evidence that alternative cell types are suitable for delivery to infarcted myocardium, specifically mesenchymal stem cells found in mononuclear bone marrow cells (See Strauer et al, Pg. 1916, col. 2-Pg 1917, col. 1). Strauer et al teach several fractions of mononuclear bone marrow cells contribute to the regeneration of necrotic myocardium and vessels; furthermore, Strauer et al showed substantial success using the bone marrow cells, including decreased infarct region size, increased wall motion velocity and decreased perfusion defects (See Strauer et al, Pg. 1915, col. 1-2). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to perform the method of Dinsmore, using non-antigenic porcine mononuclear bone marrow cells. GGTA1 knock-out mononuclear cells could be obtained from the $GGTA1^{-/-}$ pigs created by Gustafsson. Use of transgenic porcine bone marrow

cells would be desirable in patients that are unable to harvest autologous bone marrow, such as patients with compromised immune systems due to chemotherapy or autoimmune diseases. One would expect success using GGTA1 knock-out swine bone marrow for xenotransplantation into humans because Dinsmore teach porcine cells that have been altered to reduce or eliminate antigenic epitopes are suitable for use in human patients, and Strauer et al teach mononuclear bone marrow cells do successfully regenerate damaged infarcted myocardium.

Finally, though neither Dinsmore nor Gustafsson teach the GGTA1 knock-out cells to carry a nucleic acid encoding a detectable polypeptide operably linked to a promoter, such reporter systems are well known in the art. For example, in a similar method of transplanting cardiomyocytes to infarcted myocardium, Etzion et al teach using cardiomyocytes that had been transfected with recombinant adenovirus carrying the nuclear reporter gene *LacZ*, encoding for β-galactosidase (See Etzion et al, Pg. 1324, col. 2 and Fig. 1(d)). Use of the transfected cells allows one to identify newly incorporated cells in post-mortem examination, as the X-gal staining reveals blue nuclei, indicating that the *LacZ* gene was expressed; the *LacZ* must be operably linked to an operator for proper expression; therefore the nucleic acid encoding the detectable β-galactosidase was operably linked to a promoter. Use of a similar reporter polypeptide could be useful in the method of Dinsmore for the same reason, it would allow post-mortem determination of the extent of xenographic cellular uptake and integration; thus one of ordinary skill in the art would be motivated to transfect the GGTA1 knock-out swine cardiomyocytes with the nuclear reporter gene *LacZ* in order to perform post mortem examination. One would expect success because Etzion et al teach means for transfecting cardiomyocytes with the appropriate nucleic acid construct.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 19-22 and 63-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Salo (US 2003/0105493 A1), in view of Dinsmore (US Patent 5,979,449), and further in view of Gustafsson et al (US Patent 6,153,428).

Applicant's claim 19 is directed to a method, comprising identifying an infarct region within a ventricle of a subject; applying a pacing therapy to the ventricle to pre-excite the infarct region to contract during systole at a time before contraction of the ventricle; and percutaneously delivering at least one structurally reinforcing component to the infarct region after application of the pacing therapy. Claim 20 requires the at least one structurally reinforcing component to comprise α-1,3-galactosyltransferase (GGTA1) knock-out swine cells. Claim 21 requires the pacing therapy to comprise a bradycardia pacing algorithm. Claim 22 requires the method of claim 19 to further comprise modifying the pacing therapy based upon sensed measurements; claim 63 requires the sensed measurement to comprise wall motion during the cardiac cycle; claim 64 requires the sensed measurement to comprise impedance signals from a paced region and a non-ischemic region; claim 65 requires the sensed measurement to comprise a change in a wall thickness of a paced region. Claim 67 requires the donor cells to comprise stem cells. Claim 68 requires the structurally reinforcing component to have a property that stimulates a healing response in the ventricle.

Various methods were known at the time of the current invention on how to treat myocardial infarctions caused by ischemia; some methods focused on reducing the ventricular remodeling that follows myocardial infarction, while other methods focus on repairing the infarcted zone before severe ventricular remodeling took place.

For example, Salo teaches a method for minimizing the ventricular remodeling that normally follows a myocardial infarction, comprising identifying an infarct region within a ventricle of a subject by any of a number of means, including ultrasonic imaging, PET scans, thallium scans, and MRI perfusion scans (See Salo, Pg. 2, paragraph 0016); and applying a pacing therapy to sites in proximity to the infarct

to pre-excite the infarct region in a manner that lessens the mechanical stress to which the infarct region is subjected, thus reducing the stimulus for remodeling (See Salo, Pg. 1, paragraph 0006). Salo teaches the pacing therapy can comprise a bradycardia pacing algorithm, such as an inhibited demand mode or a triggered mode (See Salo, Pg. 2, paragraph 0015 & Pg. 3, paragraph 0020) (Claim 21). Salo teach that pacemakers used for such pacing therapies includes sensors and controller means to modify the pacing pulses in response to changing readings from the sensors (See Salo, Pg. 3, paragraph 00017) (Claim 22). Such sensor measurements can include impedance between pairs of electrodes, detection of wall motion during cardiac cycle, or changes in wall thickness (See Salo, Pg. 4, paragraph 0023) (Claims 63-65). Salo teaches that pre-exciting the infarct region during systole, before contraction of the ventricle as imitated by the His Purkinje conduction networks, results in a decreased preload and after load, which decreases the mechanical stress experienced by the region; thereby lessening the metabolic demands of the region and can effectively prevent or minimize the infarct remodeling (See Salo Pg. 2, paragraphs 0012-0014).

Alternatively, Dinsmore teaches a method for replacing the damaged myocardial tissue with healthy tissue by implantation of porcine cardiomyocytes into the damaged myocardium (See Dinsmore, col. 3, ln 23-55). Dinsmore teaches porcine cardiomyocytes are the preferred tissue donor source for xenotransplantations to humans when syngeneic human tissue is unavailable, due to greater availability of swine tissue compared to human tissue, similarity in organ size between the tissues, reduced risk of zoonotic infections and reduced ethical concerns (See Dinsmore, col. 1-2). Dinsmore teaches transplantation of porcine cardiomyocytes into the heart of a human subject results in replacement of lost cardiomyocytes (which is being considered a healing response in the ventricle).

Dinsmore recognizes xenotransplantations run a high risk of immunorejection due to species-specific antigens; therefore in order to reduce the risk of immunorejection of the swine cardiomyocytes Dinsmore suggest altering the cardiomyocyte such that an antigen on the cardiomyocyte surface which is capable of stimulating an immune response is altered to inhibit rejection of the cardiomyocyte upon

introduction into the human subject (See Dinsmore, abstract & col. 9, ln 56-col. 24). In one embodiment Dinsmore teaches altering the Gal(α1,3)Gal epitope, either by removal or the epitope from the surface of the cells by enzymatic or chemical cleavage or by inhibiting the formation of the epitope by inhibiting the activity of an alpha-1,3-galactosyltransferase within the cell. Therefore, based on the teaching of Dinsmore to inhibit the formation of the Gal(α1,3)Gal epitope on the cell surface to reduce potential immunorejection, it would have been well within the purview of one of ordinary skill in the art at the time the invention was made to go one step further so as to use α-1,3-galactosyltransferase (GGTA1) knock-out swine cells, wherein both copies of the GGTA1 gene have been disrupted. Such GGTA1 knock-out swine cardiomyocytes were known at the time of the invention, for example, Gustafsson et al (See Gustafsson et al col. 2, ln 19-33 & col. 6, ln 2-5). GGTA1 knock-out swine cells that have both copies of the GGTA1 gene have been disrupted cannot produce any GGTA1, and thus cannot form the antigenic Gal(α1,3)Gal epitopes at all. Clearly one of ordinary skill in the art will recognize that use of GGTA1 knock-out cells would provide superior inhibition of the antigenic Gal(α1,3)Gal epitopes compared to the methods of Dinsmore, which involve suppression of the GGTA1 gene or inhibition of the alpha-1,3-galactosyltransferase enzymes, as the knock-out cells are incapable of producing the epitopes, whereas the as the methods of Dinsmore only provide reduced epitope formation. One would expect success using the GGTA1 knock-out swine cardiomyocytes of Gustafsson in the method of Dinsmore because Gustafsson teaches the transgenic GGTA1 knock-out cells can be used as a source of cells for xenotransplantation (See Gustafsson et al, col. 5, ln 58-col. 6, ln 9).

Regarding the means of cell delivery, Dinsmore teaches the porcine cardiomyocytes can be delivered to the subject by any appropriate route; specifically they suggest direct injection into the ventricular myocardium or injection through use of tubes, catheters, etc (See Dinsmore, col. 13, ln 19-64). In the examples Dinsmore teaches direct injection during open chest surgery (See Dinsmore, Example 2, col. 19-20). However, in order to reduce the invasiveness and risk associated with open heart surgery, it

would have been obvious to one of ordinary skill in the art to alternatively deliver the cells via percutaneous transluminal coronary angioplasty (PTCA). Strauer et al teach PTCA is desirable for delivering cells to infarcted myocardium in human patients because it allows the maximum amount of cells to contact and enrich the infarct tissue and peri-infarct zone during a single treatment (See Strauer et al, Pg. 1917, col. 1). Therefore, based on the teachings of Strauer et al, it would have been obvious to one of ordinary skill in the art to deliver the GGTA1 knock-out swine cardiomyocytes to the infarcted region via percutaneous transluminal coronary angioplasty; one would have expected success because Strauer et al teach PTCA is superior to intraventricular injection and it is less invasive then direct injection during open-heart surgery.

Still further, though Dinsmore focuses on delivery of cardiomyocytes, Strauer et al provides evidence that alternative cell types are suitable for delivery to infarcted myocardium, specifically mesenchymal stem cells found in mononuclear bone marrow cells (See Strauer et al, Pg. 1916, col. 2-Pg 1917, col. 1). Strauer et al teach several fractions of mononuclear bone marrow cells contribute to the regeneration of necrotic myocardium and vessels; furthermore, Strauer et al showed substantial success using the bone marrow cells, including decreased infarct region size, increased wall motion velocity and decreased perfusion defects (See Strauer et al, Pg. 1915, col. 1-2). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to perform the method of Dinsmore, using non-antigenic porcine mononuclear bone marrow cells. GGTA1 knock-out mononuclear cells could be obtained from the $GGTA1^{-/-}$ pigs created by Gustafsson. Use of transgenic porcine bone marrow cells would be desirable in patients that are unable to harvest autologous bone marrow, such as patients with compromised immune systems due to chemotherapy or autoimmune diseases. One would expect success using GGTA1 knock-out swine bone marrow for xenotransplantation into humans because Dinsmore teach porcine cells that have been altered to reduce or eliminate antigenic epitopes are suitable

for use in human patients, and Strauer et al teach mononuclear bone marrow cells do successfully regenerate damaged infarcted myocardium.

At the time the invention was made it would have been obvious to one of ordinary skill in the art to combine the two different treatments described above to provide superior therapy to patients with myocardial infarction due to ischemia. It would have been obvious to first apply the pacing therapy of Salo, such as the bradycardia pacing algorithm, in order to decrease the mechanical stress experienced by the region, thereby effectively minimizing the degree of infarct remodeling; then after the infarct region is stabilized in size, apply the cell transplant treatment of Dinsmore, specifically using the non-antigenic GGTA1 knock-out swine cells taught by Gustafsson et al, to repair and replace damaged tissue in and around the infarction. One of ordinary skill in the art would have been motivated to combine the two therapies because both were known at the time of the invention to be effective treatments for myocardial infarction. A combination of two sequential treatments, each known for treatment of different aspects of the same disease, with no expectation for negative interaction between the two treatments, would be obvious to one of ordinary skill in the art. The idea of first minimizing the damaged area, and then replacing the damaged area with healthy tissue, when methods of performing both steps are known, would be obvious; motivation for combining the treatments would come from the desire to provide the most effective treatment to repair and regenerate the myocardial tissue following ischemia. One would expect success combining the known treatments because Salo and Dinsmore each teach success with their treatments individually, and there is no evidence or reason to believe that the combined treatments would produce negative interactions. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise

extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5 and 7 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, and 4 of copending Application No. 10/414,602. Although the claims of copending Application 10/414,602 are not identical, they are not patentably distinct from the current application because current claims 1, 5 and 7 anticipate copending claims 1, 2, and 4, respectively. Though the current claim 1 describes a specific cell line, GGTA1 knock-out swine cells, the cells read on a "structurally reinforcing agent" as described in the copending application.

Additionally, claims 1 and 5 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2 and 3 of copending Application No. 10/414,767. Although the claims of copending Application 10/414,767 are not identical, they are not patentably distinct from the current application because it would have been obvious to one of ordinary skill in the art to percutaneously deliver an implant comprising cells as the solid material to the infarct region for the purpose of reinforcing the weakened infarct region and increasing the compliance of the ventricle. One of ordinary skill in the art would have been motivated to deliver an implant comprising cells in order to rebuild and strengthen the weakened area, the cells provided in the implant would then be expected to develop into new tissue to rebuild the region.

These are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Response to Arguments

Applicants arguments received in the reply filed 17 October 2005 have been fully considered. Applicant's arguments are directed to the new limitations presently in the claims; the new limitations have been addressed in the rejections above.

Regarding the rejection under 35 USC 103(a) over Salo (US 2003/0105493 A1), applicants state that at the time the application was filed the application and Salo were owned by the same entity or subject to an obligation of assignment to the same entity, and thus Salo cannot preclude patentability under 35 USC 103(c).

However, in order to be excluded by 35 USC 103(c) a statement must be made stating that the invention as filed must was commonly owned or subject to an obligation of assignment to the same entity at the time the invention was *made*, not at the time the application was filed.

Furthermore, in the instant case it is noted that the current application is subject to assignment to *Advanced Cardiovascular Systems, Inc*, as recorded in the assignment data of the application, in contrast Salo (US 2003/0105493, now US Patent 6973349) is subject to assignment to *Cardiac Pacemakers, Inc*, as recorded in the assignment data of that application. In a telephone inquiry, initiated by the examiner, applicant's representative, William Babbitt, explained that both Advanced Cardiovascular Systems, Inc and Cardiac Pacemakers, Inc are owned by a parent company. However, due to the lack of evidence present, in the form of documentation of assignment to this parent/umbrella company in either the applications, applicants are required to provide objective evidence of common ownership by the parent company. Such evidence may consist of: A) Reference to assignments recorded in the U.S. Patent and Trademark Office in accordance with 37 CFR Part 3 which convey the entire rights in the applications to the same person(s) or organization(s); (B) Copies of unrecorded assignments which convey the entire

rights in the applications to the same person(s) or organization(s) are filed in each of the applications; (C) An affidavit or declaration by the common owner is filed which states that there is common ownership and states facts which explain why the affiant or declarant believes there is common ownership, which affidavit or declaration may be signed by an official of the corporation or organization empowered to act on behalf of the corporation or organization when the common owner is a corporation or other organization; and (D) Other evidence is submitted which establishes common ownership of the applications. Until such evidence has been supplied to prove common ownership at the time the invention was made, the Salo reference is not excluded under 35 USC 103(c).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER